

Epidemiological study in Brazilian women highlights that syphilis remains a public health problem

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ABSTRACT

Syphilis, an infectious disease considered a global public health concern, can cause stillbirths and neonatal deaths. This highlights the importance of continuous surveillance studies among women of reproductive age. A cross-sectional study was carried out to analyze the prevalence and risk factors associated with *Treponema pallidum* infection in women assisted by primary health care units in Dourados, a city located in Mato Grosso do Sul State, Brazil, which borders Paraguay. A questionnaire was applied to a population-based sample, blood samples were collected for syphilis testing and multivariable analyses were performed to screen associations with *T. pallidum* infection. The prevalence of *T. pallidum* infection was 6.04%. Bivariate analysis showed that women referring multiple sexual partners (χ^2 : 6.97 [p=0.014]), income less 2 minimal wages (χ^2 : 15.93 [p=0.003]), who did not have high school (χ^2 : 12.64 [p=0.005]), and reporting history of STIs (χ^2 : 7.30 [p=0.018]) are more likely to have syphilis. In the multivariate analysis, a highest prevalence ratio was observed in women with income less than 2 minimal wages (PR: 0.96 [95% CI: 0.85 - 0.97]), and who did not have high school (PR: 0.94 [95% CI: 0.90 - 0.98]). In addition, 80% of the women reported irregular use of condoms and 63.89% declared having sexual intercourses with multiple partners, which creates more opportunities for the transmission of the infection. These results highlight the need for healthcare systems to implement initiatives to monitor syphilis screening and the commitment of patients and their sexual partners to the treatment in order to achieve a decrease of new cases.

KEYWORDS: Risk factors. Syphilis. Women. Primary health.

INTRODUCTION

Syphilis is an infectious disease caused by the bacterium *Treponema pallidum* subspecies *pallidum*¹. Risky sexual behaviors are a frequent cause of this disease. Infected mothers can also transmit syphilis to their offspring during pregnancy or childbirth. Congenital syphilis is often fatal and can result in prematurity, low birth weight and congenital deformities². This disease represents a global concern, as it can cause neurological, cardiovascular and congenital complications. Syphilis can also facilitate HIV transmission, leading to increased rates of adverse outcomes¹.

Acquired syphilis refers to infection by *T. pallidum* acquired through sexual intercourse, intimate contact or through sharing objects. Syphilis is a public health problem, especially in pregnant women, due to the risk of transmission to the fetus causing neurosyphilis, a frequent cause of death due to syphilis^{3,4}. The number

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of cases of syphilis in women has grown in some regions of the world^{5,6}. In Brazil, the number of acquired syphilis increased 28% between 2017 and 2018. The prevalence rates of acquired syphilis more than tripled, being 26.66/100,000 inhabitants in 2013 to 81.40/100,000 in 2017; the cases in pregnant women more than doubled in the same period, with a rate of 7.11/ 100,000 inhabitants in 2013 to 16.85/ 100,000 in 2017⁷. Mato Grosso do Sul State recorded the second highest detection rate (163.0 cases/ 100,000 inhabitants), a higher number than the national average rate (75.8/ 100,000 inhabitants)⁸. Many countries, including Brazil, are committed to reducing syphilis^{9,10}. Thus, monitoring *T. pallidum* can contribute to the strategic planning for a better prevention and control of this infection.

Dourados, a city in Mato Grosso do Sul, a State located in Midwest Brazil that borders Paraguay and Bolivia, with a population of 2.5 million people is subjected to some factors that may expose the population to a higher risk of sexually transmitted infections (STIs), such as the proximity to an international border, illegal drugs trafficking, as well as the presence of indigenous and prison populations. Therefore, epidemiological studies in these locations could be useful to strengthen actions to prevent, detect and treat syphilis. Furthermore, it could lead to surveillance actions involving binational efforts. The purpose of this study was to determine the prevalence of *T. pallidum* infection and associated variables in women over 18 years old, attending primary health units in the city.

MATERIAL AND METHODS

Type of study and sample size calculation

A cross-sectional study was carried out from October 2015 to August 2016, in women attending primary health care units of Dourados, the second largest city of Mato Grosso do Sul State, with an estimated population of 222,949 inhabitants¹¹. According to the Notifiable Diseases Information System (SINAN, Brazil), Dourados has 36 primary health units, 28 of them located in urban areas, divided in four regions (North, South, East, West). The sample size was calculated using a national average prevalence of 3% for syphilis⁷, with a variation of 1%, considering the accuracy of 1.50% and confidence level of 95%, resulting in a minimum sample of 497 women.

Study participants

The present study included women who were 18 years old or more, who attended primary health care units and signed an informed consent form. Women under 18 years

old or those who refused to sign the consent form were excluded. Sample collection and randomization was performed using the cluster determined by the primary health care unit according to its location, divided by regions, considering the number of people served by it. Thus, the city was divided into eight clusters, covering a primary health care unit, being: PHU Vila Rosa, PHU Cabeceira Alegre, PHU Piratininga, PHU Joquei, PHU Parque do Lago II, PHU Vila Matos, PHU Agua Boa and PHU Seleta (Figure 1). The sample collection was performed from October 2015 to August 2016. Women who sought the primary health care unit were invited to participate in the study, according to a numeric balance of each region to comprise a heterogeneous population representative of the city.

Data and blood collection

Each participant underwent an interview in which a standardized questionnaire was used. The following variables were obtained during the interview: age, partner status (fixed partner for more than 5 years), education (illiterate, basic education, high school or graduation), drug use, risky sexual behavioral (sex with a drug user, sex with an injectable drug, sexual partner with HIV), STI history or other parameters indicative of sexually-transmitted infection (HIV positive, syphilis positive, vaginal discharge, wart in the genital region, genital ulcer disease, hands and feet ulcer disease), blood transfusion, tattoos, piercings, previous surgery, time served in prisons, and self-reported mental illness. The participant's skin color (white, black, Asian, or mixed) was self-reported. Categorical variables were represented as "Yes" or "No", and numerical variables were categorized later.

After appropriate antisepsis, a 10 mL sample of peripheral venous blood was obtained using a vacuum tube system. The sample was sent to the Health Sciences Laboratory, at the Federal University of Grande Dourados, where it was processed to obtain serum samples stored at -20 °C for the serological assays.

Serological testing

The serological diagnosis was determined by the Enzyme-Linked Immunosorbent Assay (ELISA) (ICE*Syphilis, DiaSorin, Saluggia, Italy) following the manufacturer's instructions. ELISA-reactive samples were serially diluted and titrated to detect anticardiolipin antibodies using the Venereal Disease Research Laboratory (VDRL) test (Abbott Murex, Dartford, UK). All tests were performed at the Health Sciences Research Laboratory

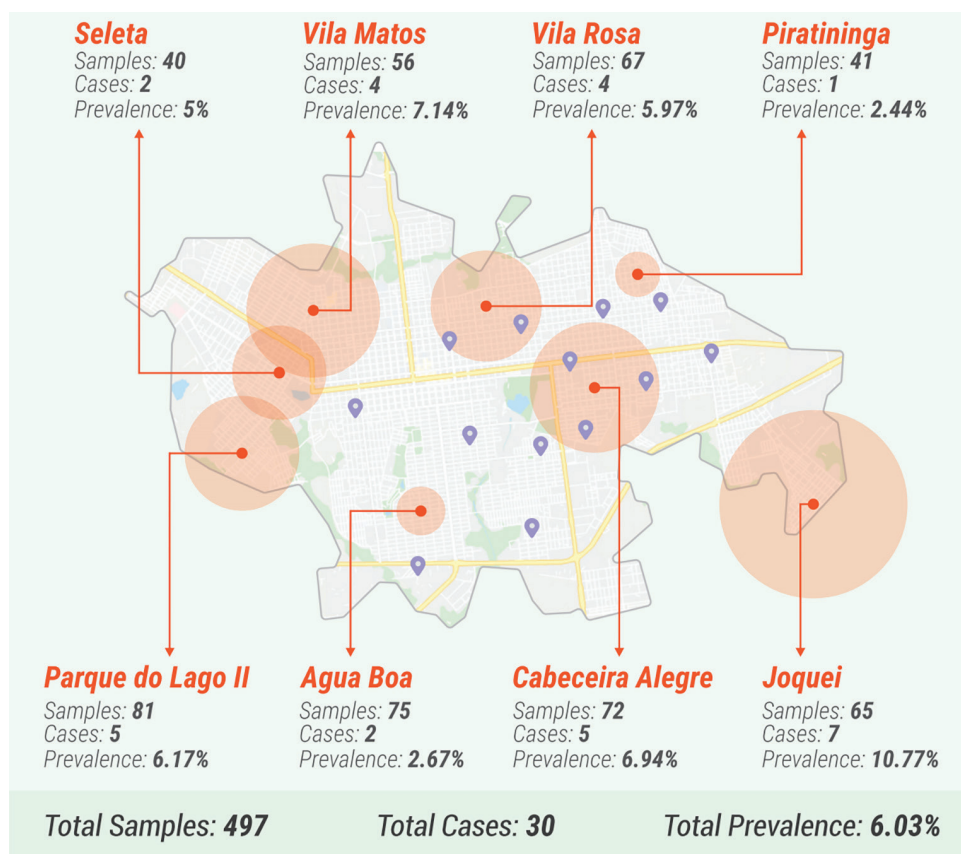


Figure 1 - Primary health care unities in urban areas from Dourados, Mato Grosso do Sul State, sample collection locations, prevalence of syphilis per health care unit evaluated. Blue dots are the primary health care units that were not included in this study and the red dots are the ones included.

of Universidade Federal da Grande Dourados. A team of previously trained health professionals performed the interviews, data collection and tests. Patients were considered to have syphilis when they were reagent to treponemal and non-treponemal tests according to reference intervals recommended by the manufacturers. All subjects received the results of their serological tests individually and a specialist in infectious diseases physician prescribed appropriate treatment to those with results indicating acquired syphilis. All new cases of syphilis identified were reported to the Notifiable Disease database (Sistema de Informacao de Agravos de Notificacao, SINAN).

Statistical analysis

Data based on questionnaires and biological test results were recorded, double-checked and inserted into the online Research Electronic Data Capture (REDCap) database. The SAS version 9.2 (SAS Institute Cary, North Carolina, USA) was used to analyze the univariate and multivariate models. Descriptive analyzes of sociodemographic, behavioral characteristics and frequency of syphilis were performed. The prevalence of *T. pallidum* infection was

expressed as the percentage among the screened women and the Clopper-Pearson exact test was used to calculate the binomial confidence interval. These analyzes were performed using the SPSS version 20 (IBM, Armonk, NY, USA). The dependent variable was to have or not syphilis.

The independent variables were analyzed and received appropriate treatment. A descriptive analysis of independent variables was performed, in which measures of central tendency were used for quantitative variables (age) and proportions (%) and 95% confidence intervals for categorical variables. Then, a bivariate analysis was performed with Pearson's chi-square test and Fisher's exact test for categorical variables. In the adjusted analysis, Poisson regression was used through a robust variance estimator and logarithmic linking function, and results were expressed in prevalence ratios (PR) and confidence intervals (CI). The variables with $p < 0.2$ in the bivariate analysis using the χ^2 test were inserted into the regression model, the variables that were not dichotomous were regrouped (Education [0. None or low; 1. Medium or high] and income [0. < 2 wages; 1. > 2 wages]). Multicollinearity analysis (VIF < 2 and tolerance > 0.6) was performed. For the quality of the adjustment, the likelihood test, Wald's hypothesis test

and residual analysis ($X^2(3) = 19,779$; $p < 0.001$) were used. The variables remained in the model if $p < 0.05$.

Ethical approval

This study complied with the requirements of the Research Ethics Committee of the Federal University of Grande Dourados (Nº 1.372.627/2015). All eligible participants provided written informed consent before taking part in the study. The serological test results were reported directly to the women by a medical doctor who also provided further orientation for the treatment.

RESULTS

Socio-demographic factors and risk behaviors

In this study, 513 women were invited to participate and 497 (96.88%) agreed with the interview and provided blood samples. The socioeconomic profile of these women was: black or of mixed ethnicity women (51%), low educational level (49.5%), with an income below a minimum wage (39%), 81% declared to be in a stable relationship for more than 5 years and 58.75% reported that they did not use a condom during sexual intercourse (Table 1).

Table 1 - Socio-demographic, risk behaviors and prevalence of syphilis in 497 women attended in the primary health care system.

Variable	N	(%)	Syphilis	(%)	95% CI	χ^2	<i>p-value</i>
Sociodemographic characteristics							
Age, years, mean (\pm SD)							
41.85 (13.94)	497	(100)	30	(6.04)	4.01 - 8.51		
Family Basic Health Unities							
Vila Rosa	67	(13.48)	4	(5.97)	1.65 - 14.59	5.30	0.622
Cabeceira Alegre	72	(14.48)	5	(6.94)	2.29 - 15.47		
Piratininga	41	(8.24)	1	(2.44)	0.00 - 12.86		
Joquei	65	(13.07)	7	(10.77)	4.44 - 20.94		
Parque do Lago II	81	(16.29)	5	(6.17)	2.03 - 13.82		
Vila Matos	56	(11.26)	4	(7.14)	1.98 - 17.29		
Agua Boa	75	(15.09)	2	(2.67)	0.32 - 9.30		
Seleta	40	(8.04)	2	(5.00)	0.61 - 16.92		
Educational level							
Illiterate	23	(4.62)	3	(13.04)	2.78 - 33.59	12.64	0.005
Basic education	228	(45.87)	21	(9.21)	5.79 - 13.73		
High school	178	(35.81)	6	(3.37)	1.25 - 7.19		
Graduation	68	(13.68)	0	(0)	0		
Ethnicity							
White	235	(47.38)	14	(5.96)	3.29 - 9.79	2.28	0.516
Black	38	(7.66)	4	(10.53)	2.94 - 24.80		
Asian	8	(1.61)	1	(12.50)	0.32 - 52.65		
Mixed Black and White	216	(43.35)	11	(5.12)	2.58 - 8.97		
Occupation							
Housewife	170	(34.20)	11	(6.47)	3.27 - 11.28	1.28	0.732
Cleaning lady	19	(3.82)	0	(0)	0		
Student	17	(3.42)	1	(5.88)	0.15 - 28.69		
Other jobs	291	(58.55)	18	(6.19)	3.71 - 9.60		
Income (Minimal wage)							
None	143	(28.77)	8	(5.59)	2.45 - 10.73		
One or less	51	(10.26)	2	(3.92)	0.48 - 13.46		
Between one and two	136	(27.36)	17	(12.50)	7.45 - 19.26		

Table 1 - Socio-demographic, risk behaviors and prevalence of syphilis in 497 women attended in the primary health care system (cont.)

Variable	N	(%)	Syphilis	(%)	95% CI	χ^2	<i>p</i> -value
Between two and three	142	(28.57)	3	(2.11)	0.44 - 6.05		
Three or more	25	(5.03)	0	(0)	0		
Sexual and behavioral history							
Stable partner	405	(81.89)	19	(4.67)	2.83 - 7.17	-	-
Multiple sexual partners	92	(18.11)	11	(11.96)	6.12 - 20.39	6.97	0.014*
History of STI(s)	37	(7.64)	6	(16.22)	6.19 - 32.01	7.30	0.018*
HIV positive	4	(0.81)	0	(0)	0	-	-
Syphilis positive	5	(1.06)	5	(100)	47.82 - 100	-	-
Vaginal discharge	293	(58.95)	17	(5.80)	3.42 - 9.13	-	-
Wart in the genital region	55	(11.07)	3	(5.45)	1.14 - 15.12	-	-
Genital ulcer disease	62	(12.47)	8	(12.90)	5.74 - 23.85	5.88	0.391*
Hands and feet ulcer disease	6	(1.21)	1	(16.67)	0.42 - 64.12	1.21	0.313*
Sex with a drug user	36	(7.24)	1	(2.78)	0.00 - 14.53	-	-
Sex with an injectable drug	9	(1.81)	0	(0)	0	-	-
Sexual partner whit HIV	2	(0.45)	0	(0)	0	-	-
Sexual preference							
Heterosexual	495	(99.60)	30	(6.06)	4.13 - 8.54	-	-
Homosexual	2	(0.4)	0	(0)	0	-	-
Condom use							
All women						0.20	0.671
Always	95	(19.11)	6	(6.32)	2.35 - 13.24		
Sometimes	110	(22.13)	5	(4.55)	1.49 - 10.29		
Never	292	(58.75)	19	(6.51)	3.96 - 9.97		
Alcohol, drugs and other risk factors							
Smoker	56	()	5	(8.93)	2.96 - 19.62	0.85	0.371*
Alcohol use	209	(42.05)	6	(2.87)	1.06 - 6.14	-	-
Illegal drugs use	21	(4.23)	1	(4.76)	0.12 - 23.82	0.59	0.395*
Blood transfusion	43	(8.88)	6	(13.95)	5.30 - 27.93	5.20	0.036*
Tattoo	89	(17.91)	2	(2.25)	0.27 - 7.88	2.74	0.138*
Piercing	55	(11.07)	1	(1.82)	0.00 - 9.72	1.94	0.233*
Shares syringe/needle	6	(1.21)	0	(0)	0	-	-
Without sterilized tools	244	(49.09)	0	(0)	0	-	-
Surgery last year	55	(11.07)	3	(5.45)	1.14 - 15.12	-	-
Hepatitis B vaccine	282	(72.12)	14	(4.96)	2.74 - 8.19	-	-
Positive Serology							
Elisa – Treponemic Test	36	(7.24)					
VDRL – Non-treponemic Test	30	(6.04)					
VDRL Titration							
½ to ¼	24	(82.77)					
> 1/8	6	(17.23)					

STI = Sexually-Transmitted Infections; HIV = Human Immunodeficiency Virus; ELISA = Enzyme-Linked Immunosorbent Assay; VDRL = Venereal Disease Research Laboratory. *Exact Fisher Test. Highlighted $p \leq 0.2$.

Table 2 - Bivariate analysis and multivariate Poisson regression analysis on the prevalence ratio of syphilis among women attended in the primary health care system.

Variables	PR	IC 95%	p-value	PR adjusted	IC 95%	p-value
Education						
High school and graduation	0.957	0.918 - 0.998	0.039	0.940	0.902 – 0.980	0.004
Income less than 2 minimal wages	0.940	0.918- 0.980	0.002	0.958	0.924 - 0.993	0.019
Sexual history						
Multiple sexual partners	1.083	1.001 - 1.171	0.047	0.937	0.866 - 1.014	0.106
Genital ulcer disease	0.917	0.832 - 1.012	0.085	-	-	-

PR = Prevalence ratio. Highlights $p \leq 0.05$.

The prevalence of *T. pallidum* infection among women was 6.04% [95% CI: 4.11-8.50]. The highest prevalence rates were found in women living in the Joquei neighborhood 10.77% [95% CI: 4.44-20.94], illiterate women 13.4% [95% CI: 2.78-33.59], black women 10.53% [95% CI: 2.94-24.80] and without a stable sexual partner 11.96% [95% CI: 6.12-20.39]. Regarding behavioral factors, the highest prevalence rates were found among women that had history of STI (16.22% [95% CI: 6.19-32.01]), genital ulcers (12.90 % [95% CI: 5.74-23.85]), without a stable sexual partner and referring irregular use of condoms during sexual intercourse (24.24% [95% CI: 11.09-42.26] and who had a blood transfusion (13.95% [95% CI: 5.30-27.93]) (Table 1). All cases were reported to healthcare services to provide appropriate treatment.

The bivariate analysis showed that women with multiple sexual partners (χ^2 : 6.44 [p=0.014]), income less 2 minimum wages (χ^2 : 15.93 [p=0.003]), who did not have high school (χ^2 : 12.64 [p=0.005]), and who reported history of STIs (χ^2 : 7.30 [p=0.018]) are more likely to have syphilis (Table 1). In the bivariate Poisson regression model, the prevalence was higher among women who did not have high school (PR 0.95 [95% CI: 0.91-0.99]), with income less 2 minimal wages (PR 0.94 [95% CI: 0.91-0.98]), and with multiple sexual partners (PR 1.08 [95% CI: 1.01-1.17]). In the multivariate analysis, the highest prevalence ratio was observed in women with income less 2 minimal wages (PR: 0.96 [95% CI: 0.85-0.97]), and who did not have high school (PR: 0.94 [95% CI: 0.90-0.98]). (Table 2).

DISCUSSION

In the present study, we described the prevalence and the factors associated with *T. pallidum* infection among women. The number of occurrences was higher than the global prevalence, which estimated a prevalence of 0.5% among women aged 15-49 years. The prevalence rate in our study is similar to the one found in women in vulnerable

situations^{12,13}. This high prevalence among women is a concern since, in an eventual pregnancy, *T. pallidum* can infect the fetus and lead to adverse outcomes when untreated, such as abortion and risk to the women's health and the child's neuropsychomotor development^{14,15}. Thus, the public health policies need to be strengthened according to the reality of these populations in an attempt to reduce the number of cases of syphilis.

We identified that 63.89% of the participants with syphilis had multiple sexual partners and 80% reported occasional condom use. These behaviors could have facilitated *T. pallidum* transmission. Moreover, the high rates of syphilis could be a potential risk for the spread of other STIs, including HIV, during unprotected sex¹⁶. The chance of transmitting HIV is five-fold increased if either partner has an ulcerative STI like syphilis^{10,11}. The lesions of this pathological condition contain an abundance of lymphocytes, which makes the infiltration of HIV more recurrent. Furthermore, the immunosuppression caused by HIV may favor the evasion of the host defense mechanisms by *T. pallidum*^{16,17}. A positive status for *T. pallidum* in patients with a previous history of STI may be associated with unprotected sex. An additional element that can increase syphilis rates may be the presence of genital ulcers. *T. pallidum* transmission rate was estimated to be 20% to 30% higher per sexual act. Besides, multiple partners increase the likelihood of transmission and dissemination of this pathogen¹⁷. It is important to note that condoms are not as effective to prevent infections that are transmitted through lesions, if it does not cover the wound¹⁸. Thus, the presence of ulcers can facilitate the occurrence of syphilis and other infectious diseases¹⁹.

Since several factors were associated with *T. pallidum* among women, it is likely that multiple approaches could contribute for the reduction of syphilis rates. An alternative to reduce the prevalence of syphilis would be to concentrate efforts for the follow-up of positive cases and the effectiveness of the treatment, as well as the sexual partners.

As widely known, diagnostic has a central role in guiding the procedure. In some cases, a specific stage of syphilis can be asymptomatic¹⁶. Thus, screening programs could be an essential preventive approach. Studies have shown that regular screening (every 3-6 months) among groups at high risk to acquire STI, can contribute for reducing the incidence of syphilis²⁰.

We showed that socioeconomic variables, such as low income and poor educational levels were frequent in this population, the same situation reported in the USA, China and Argentina²¹⁻²³. In our study, the prevalence of syphilis was higher in women with an income of less than 2 minimal wages (96%) who did not have high school (94%). These data may indicate a relationship between socioeconomic factors and the prevalence of syphilis in this population. In addition, the prevalence of syphilis was different among the evaluated primary health care units. The Joquei primary health care unit located on the outskirts of the city showed a higher positive rate (10.77%) and 70.76% had only a basic educational level. This may indicate inequalities in self-care, as well as difficulties to access and continue to seek treatment in health services. Public health has an essential role in disease prevention. However, budget cuts over the last several years may have hampered the STI preventive measures, such as a decrease in syphilis screening. Furthermore, Brazil suffered from a shortage of Benzathine penicillin G, a drug used in the syphilis treatment²⁴. Thus, these factors may also have contributed to the high prevalence of syphilis among Brazilian women. All these factors have a direct impact on the quality of services provided by primary health care units that should monitor the health of the population, as well as subsidizing educational measures that help to reduce the number of syphilis cases.

There were some limitations in this study. Firstly, it was a prospective study in one Brazilian city. Secondly, it was a convenience sample for women who sought primary health care units. This is a selection bias and may have interfered with the high prevalence found. In addition, despite the sample size being sufficient to infer the prevalence of syphilis, it was inadequate to perform stratified analyses of variables. Besides the limitations, our study provides insights on the prevalence of syphilis in Brazilian women.

The high prevalence of *T. pallidum* infection, especially in a scenario of heavy border traffic, as is the case in Dourados, has evidenced the need for interventions to reduce sexual behaviors that are associated with an increased risk of STIs in women. Thus, our study reinforces the importance of active surveillance in the primary health care through the extensive testing of patients and their sexual partners, seeking to detect symptomatic and asymptomatic syphilis cases, promoting the adequate treatment promptly. In

addition, interventions that encourage safe sexual practices could reduce *T. pallidum* transmission, as well as eventual congenital infections.

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